

## **Locus coeruleus reports changes in environmental contingencies**

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**Abstract:** The GANE model proposed by Mather et al. attempts to explain how norepinephrine enhances processing in highly activated brain regions. Careful perusal of the sparse data available from recording studies in animals shows that noradrenergic neurons are mainly excited by any change in the environment- a salient, novel or unexpected sensory stimulus, or a change in behavioral contingencies. This begets the 'network reset hypothesis' supporting the notion that NE promotes rapid cognitive and behavioral adaption

The functional significance of neuronal activity in a particular brain region or population of neurons is found in the environmental stimuli or cognitive context that drive (or inhibit) activity in those neurons. Thus we know from electrophysiological exploration that the function of primary visual cortex is to respond to light, auditory cortex to sound etc. Thalamic nuclei have likewise been delineated in terms of function. The role of prefrontal cortex in working memory was hypothesized by lesion studies but clearly demonstrated by recording neuronal activity in monkeys performing working memory tasks (Fuster, 1991; Goldman-Rakic, 1990). Likewise, single unit recording in rats performing spatial navigation tasks established the fundamental role of the hippocampus in spatial cognition (O'Keefe & Dostrovsky, 1971). One of the principle functions of neurons of the Ventral Tegmental Area is to report reward prediction error, based on recordings from this region in monkeys performing operant tasks. Thus, to gain a full understanding of the functional role of the Locus Coeruleus-Noradrenergic system (LC-NE) it is important to carefully consider what drives this small population of neurons.

Until recent biotechnological developments, the only way to achieve this was through recording activity of LC neurons in unanaesthetized animals in carefully controlled behavioral situations. Given the inaccessible pontine location and very small size of this nucleus, the task has proved to be challenging and the resultant literature quite sparse. Nevertheless, there are some studies that provide insight the goes beyond LC-NE mediation of arousal and response to salient, stressful or novel stimuli, as summarized by Mather et al. in section 4.1. Furthermore, recent advances in fMRI resolution have allowed imaging of this nucleus in humans performing complex cognitive tasks. These studies are now corroborating a role for LC in cognitive flexibility and behavioral adaptation, already demonstrated by electrophysiological studies in animals.

The earliest recordings of activity of LC in behaving rats established its role in vigilance, and its responses to salient environmental stimuli in all modalities (Aston-Jones et al, 1981). Subsequent experiments in rats and monkeys showed that LC neurons display remarkable plasticity as a function of environment contingencies. Sensory responses habituate after just a few repetition, even when initially robust, when no behavioral adaptation is required (Hervé-Minvielle & Sara, 1994). In a hole board environment, encounter with a novel object elicits a robust phasic burst of LC neurons that persists for only one or two subsequent investigations of the object (Vankov et al, 1995). Differential conditioning studies have shown that LC cells are exquisitely sensitive to stimulus-reward contingencies, showing task-related responses at the very earliest stages. At the beginning of training both conditioned stimuli and primary reward elicit phasic responses in LC neurons. After just a few trials, response to reward disappears and response to the stimulus predicting reward (CS+) increases, while responses to the neutral stimulus (CS-) decrease. These discriminative conditioned responses in LC appear many trials before any behavioral expression of learning and before task related responses emerge in the prefrontal cortex. They are not maintained during overtraining, but when contingencies change abruptly, as during extinction or reversal training, phasic LC responses are immediately reinstated, tens of trials before behavioral expression of learning (Sara & Segal, 1991; Bouret & Sara, 2004). Similar phenomena have been reported for

behaviorally-contingent LC activity in monkeys (Rajkowski et al, 1994; Aston-Jones et al. 1997).

These relatively sparse data collected from behaving rats and monkeys over a time span of 25 years led us to hypothesize that NE released in the cortex in response to a salient event or to a sudden change in environmental contingencies may act to facilitate or promote a rapid change in cortical state, ‘reset’ the active network, and drive an adaptive behavioral response (Bouret & Sara, 2005; Sara & Bouret, 2012). We have provided some preliminary evidence for a ‘reset’ action of NE, revealed by spike-triggered wave form averages of gamma filtered LFP. Gamma band synchronization (GBS) has functional roles in diverse cognitive processes including attention, stimulus processing, decision making and response timing (Bosman et al, 2014). We found a strong temporal relation between GBS and spontaneous LC bursts. In fact, LC spiking interrupts the gamma wave for about 200 ms, with the recovered GBS having increased power (Sara 2015, Fig3; Poe and Sara, Soc Neurosci, Abstract #652.16 2014).

Recent fMRI studies in humans have lent strong support to a prediction of Corbetta et al, (2008) that there should be a strong functional relation between the ventral front-parietal network, involved in ‘resetting’ attention and LC neuronal activity, given the ‘striking similarity between the environmental contingencies driving’ them. In a recent study requiring subjects to continually modify their behavior as a function of unpredictable changes in stimulus-response contingencies, switches elicited activation in a frontal-parietal network that has been implicated in task switching and error awareness, in concert with activation of the brainstem LC (von der Gablentz et al. 2015). Several other similar studies in humans have confirmed that LC is co-activated with frontal regions or has increased functional connectivity with them in cognitively demanding tasks requiring rapid shifts in allocation of attention (Sara, 2015 for review). This rapidly growing literature has strongly supported the earlier electrophysiological data from animal studies leading to the network reset hypothesis of the functional role of the LC-NE system.

The GANE model proposed by Mather et al. is complementary to the ‘reset’ hypothesis. The model provides a basis for understanding how NE biases perception and promotes synaptic plasticity and memory formation in select target regions that are engaged by current contingencies. However, the efficacy of glutamate recruitment of the LC-NE system to *enhance* processing of significant stimuli will depend, at least in part, on action potentials in LC neurons. These neurons are driven by environmental imperatives for a rapid cognitive shift and behavioral adaptation. Thus, we conclude that the overarching function of the LC-NE system is to promote rapid change in ongoing network activity (Bouret & Sara, 2005). GANE provides a testable model of how subsequent release of NE can provide selective enhancement of the reorganized network.

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